REMARKS/ARGUMENTS

Claims 1, 6 and 7 were previously pending in the present application. Claims 8-16 were previously withdrawn. Claim 1 has been amended. No new matter has been added. Entry of the current amendment to claim 1 into the file of the present application is respectfully requested as it is believed to place the entire application in condition for an allowance.

Applicants acknowledge and appreciate the explanatory comments provided by the Examiner in the Advisory Action mailed December 12, 2008. Applicants address the Examiner's grounds for rejection below.

Claim Rejections Under 35 U.S.C. §103 (Non-Obviousness Requirement)

Claims 1, 6 and 7, directed to a system for incorporating unnatural amino acids into proteins in Eukaryotic translation in isolated animal host cells, have been rejected under 35 U.S.C. § 103(a) over Kiga et al.

In response to this rejection, previous claim 1 has been further amended, without prejudice or disclaimer, to clarify that which Applicants deem to be the patentable subject matter of the present application.

E. coli lacks the A and B Box promoter sequences needed for expression in eukaryotic cells. The Examiner contends that a scientist practicing in the field would be motivated to try to use *B. stearothermophilus* suppressor tRNA (which includes the A and B Box sequences), that it would be obvious to do so, and that such a scientist would reasonably expect success in doing so. Applicants respectfully disagree with this view. *E. coli* and *B. stearothermophilus* are divergent species, each under a different set of natural selection pressures, and the conventional understanding in the field would be that cross-species combinations of the tRNA synthetase from one species (*E. coli*) with the suppressor tRNA from a distinct other species (*B. stearothermophilus*) would not likely properly work together in any gene expression system. Accordingly, a scientist in the field would not have a reasonable expectation of success from combining across these particular species and would not be motivated to invest in such efforts.

Note that even should a scientist try to incorporate and engineer A and B Box sequences into *E. coli* (in hopes of facilitating eukaryotic expression), such efforts usually result in mismatches of the base pairs within the tRNA sequence, leading to alterations in the tRNA structure itself which render the tRNA non-functional. Attempts to correct for such mismatches

in sequence and structure to create functional tRNA have been unsuccessful. See, *e.g.*, Sakamoto et al., Site-specific incorporation of an unnatural amino acid into proteins in mammalian cells, Nucleic Acids Research, 2002 (Nov.), Vol. 30, No. 21, 4692-4699 (at 4694-4695), in which scientists engineered specific mutations within the *E. coli* tRNA so as to generate the A Box within the promoter sequence (to result in *E. coli* tRNA with both A and B Box sequences), but these efforts failed to result in functional suppression activity in mammalian (Chinese hamster ovary) cells. A copy of the Sakamoto reference is being submitted concurrently with this amendment under separate cover by means of a Supplementary Information Disclosure Statement. A declaration by one of skill in the art in support of the arguments contained herein concerning the subject reference will be readily provided by Applicants, if so required by the Examiner.

The references cited by the Examiner are silent upon the issue as to how and why the suppressor tRNA specifically from *B. stearothermophilus* would overcome these difficulties and would readily work with the *E. coli* tRNA synthetase for expression in animal cells. Thus, the motivation and expectation of success in combining the *B. stearothermophilus* suppressor tRNA with *E. coli* tRNA synthetase in a eukaryotic expression system is only first offered with the present disclosure.

Furthermore, a scientist would be unlikely to specifically pursue *B. stearothermophilus* tRNA as a likely initial candidate for pursuit in such efforts, without such teaching or motivation to try it in particular. Of the over 100 genera of eubacteria whose tRNA sequences are publicly known and available (*e.g., see* http://lowelab.ucsc.edu/GtRNAdb/), 27 genera belong to Omnibacteria, which is more closely related to the genus encompassing Gram-negative *E. coli*. Accordingly, a scientist in the field would be likely to make attempts with these more closely related tRNA sequences, rather than to pursue efforts involving the more distantly related Gram-positive genus of *Bacillus*. It is unclear how it would be obvious for a scientist to skip those efforts and pursue efforts with *B. stearothermophilus* instead (and reasonably expect success for doing so).

Applicants reiterate that, to the contrary, it is only by relying upon the disclosure contained in the present application that a scientist practicing in the field would recognize the value of and be motivated to attempt and practice the current methods as recited in claim 1. Claim 1 as recited, along with pending claims 6 and 7 dependent thereto, is now believed to allay

the concerns set forth by the examiner in the Office Action and to overcome the rejection under 35 U.S.C. § 103(a). Applicants respectfully ask that the examiner reconsider the outstanding rejection under 35 U.S.C. § 103(a), in view of the amendments made to claim 1, and to deem claims 1, 6 and 7 to be in suitable condition for prompt allowance.

Summary

This Amendment is believed to overcome all of the grounds for objection and rejection set forth in the August 7, 2008 Office Action regarding this application, which should therefore be withdrawn.

If the Examiner does not agree, however, but believes that an interview would advance the prosecution of this case, the Examiner is respectfully invited to telephone Applicants' representative at the number below in order that an interview concerning this application may be scheduled.

Respectfully submitted,

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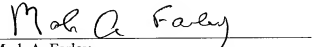

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